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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/456,306	DUSCH ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35 and 41-43* is/are rejected.

7)☒ Claim(s) *36-40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/30/01; 11/15/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 35-43 are pending in the application.

[2] Applicants' amendment to the claims, filed November 15, 2001, is acknowledged. Claim 34 has been canceled and claims 35 and 40-41 have been amended.

[3] Receipt of formal drawings, filed November 15, 2001, is acknowledged.

[4] The indicated allowability of claims 36 and 42-43 is withdrawn in view of the new rejection as set forth below.

Sequence Compliance

[5] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). See particularly page page 18, lines 11 and 13 of the specification. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the

specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

Specification/Informalities

[6] The abstract of the disclosure is objected to because it is not a single paragraph. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[7] Claims 41-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 41 is unclear in the recitation of "[a] second isolated polynucleotide" as it is unclear as to the polynucleotide that is intended as being a first isolated polynucleotide. It is suggested that applicants clarify the meaning of the claim.

[b] Claims 42-43 are indefinite in the recitation of "having a sequence identical to a segment." MPEP 2111 directs the examiner to give claims their broadest reasonable interpretation. In this case, the claims have at least two distinct interpretations: 1) in the most limited interpretation, the claims can be interpreted as oligonucleotides that are

fragments of 15-50 contiguous nucleotides of the nucleic acid of claim 36 or the nucleic acid of SEQ ID NO:1 or 2) in their broadest interpretation (in view of the open transitional phrase "having" and the indefinite term "segment"), the claims can be interpreted as oligonucleotides that have any sequence of 15-50 nucleotides. Thus, it is unclear as to scope of claimed oligonucleotides. It is suggested that applicants clarify the meaning of the claims.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[8] Claim(s) 42-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus of oligonucleotides between 15 and 50 bases in length and having a sequence that is identical to a segment of a polynucleotide encoding a polypeptide that is 95% identical to SEQ ID NO:2 or that is identical to a segment of SEQ ID NO:1. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e.,

structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the claimed genus of oligonucleotides is widely variant in both structure and function. Regarding the structural variability, in view of the broadest interpretation of the claims (see above), the oligonucleotides can comprise essentially any 15-50 nucleotide sequence. Regarding the functional variability, there is no correlation between the function of the oligonucleotides and their structures. The specification describes only a single representative species of the claimed genus, i.e., an oligonucleotide consisting of a fragment of 15-50 contiguous nucleotides of SEQ ID NO:1. The specification fails to describe any additional representative species of the claimed genus, which encompasses species that are widely variant in both structure and function, including (but not limited to) any oligonucleotide having the ability to hybridize to any nucleic acid sequence. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it is also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". As

such, the disclosure of the single representative species of oligonucleotides is insufficient to be representative of the attributes and features of *all* species encompassed by the recited genus of oligonucleotides. Given the lack of description of a representative number of oligonucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[9] Claims 36 and 42-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding SEQ ID NO:2, including SEQ ID NO:1 and an oligonucleotide consisting of from 15-50 contiguous nucleotides of a nucleic acid encoding SEQ ID NO:2, does not reasonably provide enablement for the broad scope of claimed nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP §

2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass a vast number of variants of SEQ ID NO:2 and oligonucleotides. The broad scope of claimed nucleic acids and oligonucleotides is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleic acids encoding variants of SEQ ID NO:2 and oligonucleotides broadly encompassed by the claims. In this case the disclosure is limited to a nucleic acid encoding SEQ ID NO:2, including SEQ ID NO:1 and an oligonucleotide consisting of from 15-50 contiguous nucleotides of a nucleic acid encoding SEQ ID NO:2.

- The lack of guidance and working examples: The specification provides only a single working example of the claimed nucleic acid, i.e., SEQ ID NO:1 and the specification provides only a single working example of the claimed oligonucleotide, i.e., a fragment of SEQ ID NO:1. These working examples fail to provide the necessary guidance for making and/or using the entire scope of the claimed invention. Regarding the claimed nucleic acids encoding variants of SEQ ID NO:2, the specification fails to provide guidance regarding those nucleotides of SEQ ID NO:1 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of encoding a protein maintaining the desired activity. Regarding the claimed oligonucleotides, the specification fails to provide guidance regarding those nucleotides of SEQ ID NO:1 that may be altered by substitution, addition, insertion, and/or deletion with an expectation of maintaining the ability to hybridize to a desired nucleic acid.

- The high level of unpredictability in the art: The nucleotide sequence of a nucleic acid determines its structural and functional properties. Predictability of which changes can be tolerated in a nucleic acid's sequence and obtain the desired encoded protein or hybridize to the desired target nucleic acid requires a knowledge of and guidance with regard to which nucleotides, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which the nucleic acids' structure relates to its function. The positions within an encoding nucleic acid's sequence where modifications can be made with a reasonable expectation of success in obtaining an encoded polypeptide or hybridizing to a desired target nucleic acid having the desired activity/utility are limited and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification to diminish with each further and additional modification, e.g., multiple substitutions. In this case, the necessary guidance has not been provided in the specification as explained in detail above. Thus, a skilled artisan would recognize the high degree of unpredictability that the entire scope of polynucleotides would encode a polypeptide having the desired activity or would hybridize to the desired target nucleic acid.

- The state of the prior art supports the high level of unpredictability: The state of the art provides evidence for the high degree of unpredictability in altering a protein-encoding sequence with an expectation that the protein will maintain the desired activity/utility. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been

surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247). While it is acknowledged that this reference was published in 1991, to date there is no method for reasonably predicting the effects of even a *single* amino acid mutation on a protein. The teachings of Branden et al. are exemplified by Witkowski et al. (Biochemistry 38:11643-11650).

- The amount of experimentation required is undue: While methods of generating variants of a given nucleic acid or oligonucleotide are known, it is not routine in the art to screen for all nucleic acids or oligonucleotides having a substantial number of modifications for those having the desired utility, as encompassed by the instant claims.

Therefore, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high degree of unpredictability as evidenced by the prior art, and the significant amount of experimentation required to make and/or use the broad scope of claimed nucleic acids and methods, undue experimentation would clearly be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the

desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[10] Status of the claims:

- Claims 35-43 are pending.
- Claims 36 and 41-43 are rejected.
- Claims 37-40 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
- Claims 36 and 41-43 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, first and second paragraphs as set forth in this Office action.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (571) 272-0942. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

06-10-04